Effect of leukoreduced transfusion on infection risk in trauma

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Background

- Transfusion of allogeneic red blood cells strongly associated with higher likelihood of infection and multiple organ failure
  - Trauma, cardiac surgery, elective major abdominal surgery
- Mechanism thought to be related to transfusion-related immunomodulation (TRIM)
- Experimental and some clinical evidence suggest TRIM occurs as a result of "passenger" leukocytes – 10^9/unit
  - Induction of anergy – infection risk
  - Induction of a pro-inflammatory response

Leukoreduction

- Transfusion of leukoreduced blood associated with fewer febrile transfusion reactions, lower rates of platelet alloimmunization
- Effect on infection risk, multiple organ failure inconsistent across studies
  - Cardiac surgery
  - Elective abdominal surgery

Objective

- To evaluate the effect of prestorage leukoreduced transfusion compared to standard allogeneic transfusion in patients with hemorrhage due to trauma
  - High risk for infection, multiple organ failure
  - Large transfusion requirements

Methods

- Study design
  - Double blind randomized controlled trial
  - Emergency waiver of consent
- Injured patients randomized at time of type and cross match to either:
  - Standard packed red cell transfusion
  - Leukoreduced red cell transfusion

Inclusion/Exclusion criteria

- Inclusion criteria
  - Trauma patient
  - Estimated age>17
  - Transfusion within 24 hours of injury

- Exclusion criteria
  - Active infection
  - Prisoner
  - Anticipated survival of <48 hrs (e.g. GSW to head, CPR in progress)
  - Receipt of blood products for current injury event prior to randomization
  - Rare blood types:
    - AB negative, B negative
  - Positive antibody screen
  - Prior requirement for irradiated, leukoreduced or CMV seronegative products

Randomization & blinding

- Stratified randomization based on age (<55 yrs or ≥55 yrs) and mechanism of injury (blunt/penetrating)
- Randomization performed by hospital-based transfusion support services personnel using preprinted envelopes once order for type & cross received
  - Study blood in blood refrigerators in ED for those requiring uncrossmatched blood
  - Concealed allocation
- Units labeled as "For Research Purposes Only"

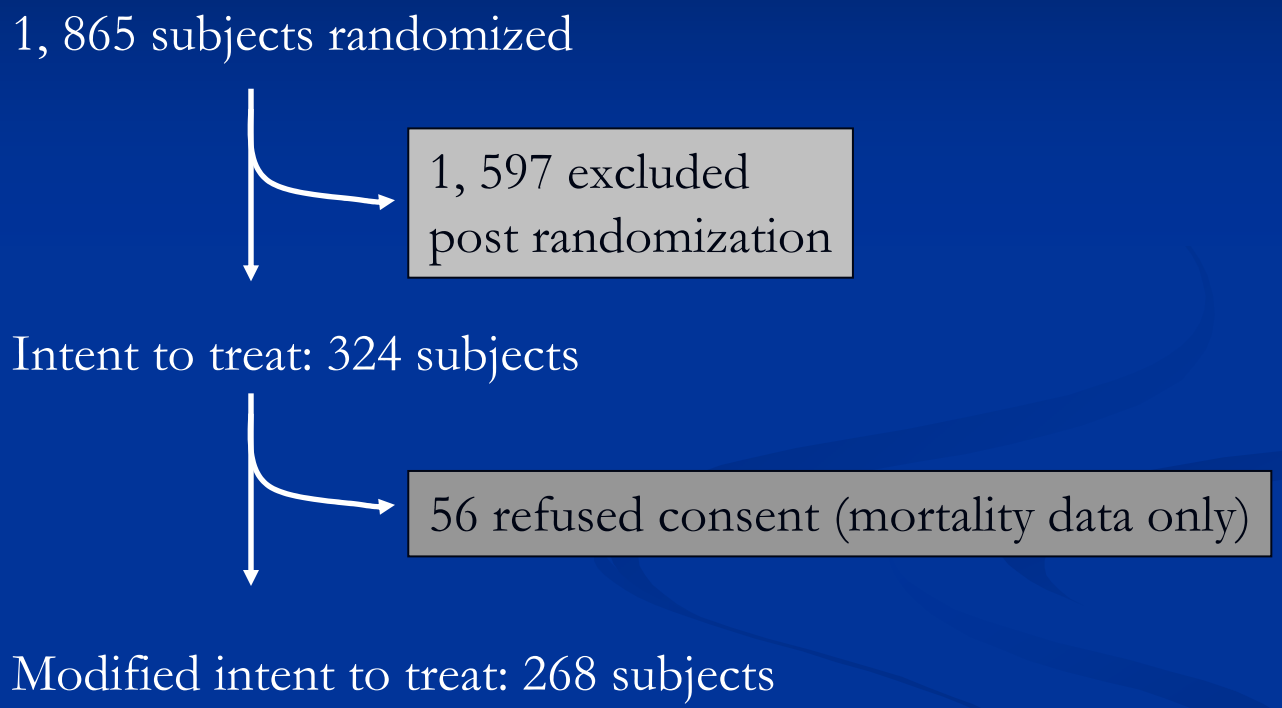
Study products

- Subjects received study blood products for the shorter of the duration of their hospital admission or 28 days
- Study products
  - Leukoreduced red cell transfusion
    - Prestorage leukoreduction within 24 hrs of collection
    - Pall filter ($<5 \times 10^6$ WBC's/unit)
- Maximum age of red cells 25 d in either arm
- Prestorage leukoreduced apheresis platelets administered when platelet transfusion necessary

Study Endpoints

- Infectious complications within 28 d of randomization
  - Post discharge followup (telephone/clinic visit)
- Sample size estimate
  - Baseline risk of infection 30%
  - Relative risk 0.40, absolute risk of 12% in leukoreduced group
  - β=0.1, α=0.05, 117 per arm
  - Inflated by ~25% for refusals/protocol violations: 150 per arm
- Secondary endpoints
  - Multiple organ failure (Marshall), mortality, ventilator days, ICU and hospital LOS

Randomization and eligibility



Post-randomization exclusions

	Standard	Leukoreduced
Not transfused within 24 hrs	674 (72)	682 (73)
Age<18 years	8 (0.86)	7 (0.75)
Not trauma	22 (2.4)	23 (2.5)
Prisoner	9 (0.96)	8 (0.86)
Prior transfusion	17 (1.8)	13 (1.4)
B- or AB- blood type	8 (0.86)	11 (1.2)
Requires CMV-, leukoreduced or irradiated blood	2 (0.21)	4 (0.43)
Low community inventory	12 (1.3)	13 (1.4)
Enrolled in field investigational drug study	1 (0.11)	4 (0.43
Unsurvivable injury	10 (1.1)	5 (0.54)
Refused consent	32 (19)	24 (15)

Baseline characteristics (MITT)

	Standard (N=136)	**Leukoreduced** (N=132)
Mean age (SD)	42.1 (18)	42.3 (19)
Male	93 (69)	87 (66)
Race		
White	116 (85)	114 (86)
Black	12 (8.8)	8 (6.1)
Other	8 (5.8)	10 (6.6)
Comorbidities		
None	91 (67)	88 (67)
Cardiovascular disease	13 (9.6)	12 (9.1)
Neurologic	6 (4.4)	2 (1.5)
COPD	8 (5.9)	5 (3.8)
Diabetes	9 (6.6)	11 (8.3)
Mechanism		
Penetrating injury	24 (18)	25 (19)

Injury severity (MITT)

	Standard (N=136)	Leukoreduced (N=132)
Injury severity score (SD)	25.5 (11)	23.9 (11)
Maximum AIS		
≤3	50 (37)	58 (44)
4	58 (43)	49 (37)
5	28 (21)	25 (19)
Shock*	68 (50)	76 (58)
Highest ED lactate (mmol/l)	4.2 (3.2)	4.1 (2.8)
Lowest ED hematocrit	27.2 (7.5)	26.5 (7.7)

*Systolic blood pressure<90 in the field or emergency department

Blood product requirements (MITT)

	Standard (N=136)	**Leukoreduced** (N=132)
Transfusion reqt's (hospitalization)		
Red blood cells	2100 (1400-3675)	2100 (1225-3500)
Fresh frozen plasma	1000 (0-2464)	961 (0-2018)
Platelets	0 (0-274)	0 (0-260)
Cryoprecipitate	0 (0-0)	0 (0-114)
Transfusion reqt's in 1st 48 hrs*		
Red blood cells	1400 (700-2450)	1400 (875-2450)
Fresh frozen plasma	985 (0-1914)	948 (0-1970)
Platelets	0 (0-250)	0 (0-250)
Cryoprecipitate	0 (0-0)	0 (0-114)
Age of transfused RBC's (days, mean$\pm$SD)	16.8$\pm$4.1	16.9$\pm$4.3

*Data presented are median (interquartile range). Transfusion requirements are presented in mls

Infectious complications (MITT)

	Standard (N=131)	Leukoreduced (N=121)	RR (95% CI)
Pneumonia			
All diagnoses	16 (12)	13 (11)	0.88 (0.42-1.8)
Invasive diagnosis only	8 (6.1)	8 (6.6)	1.08 (0.41-2.9)
Bloodstream infections	4 (3.1)	5 (4.1)	1.35 (0.36-5.0)
Surgical site infections	22 (17)	17 (14)	0.84 (0.44-1.6)
Urinary tract infections	21 (16)	14 (12)	0.72 (0.37-1.4)
Pseudomembranous colitis	4 (3.0)	0	N/A
Any infection	49 (37)	40 (33)	0.88 (0.58-1.3)

Infectious complications as a function of injury severity

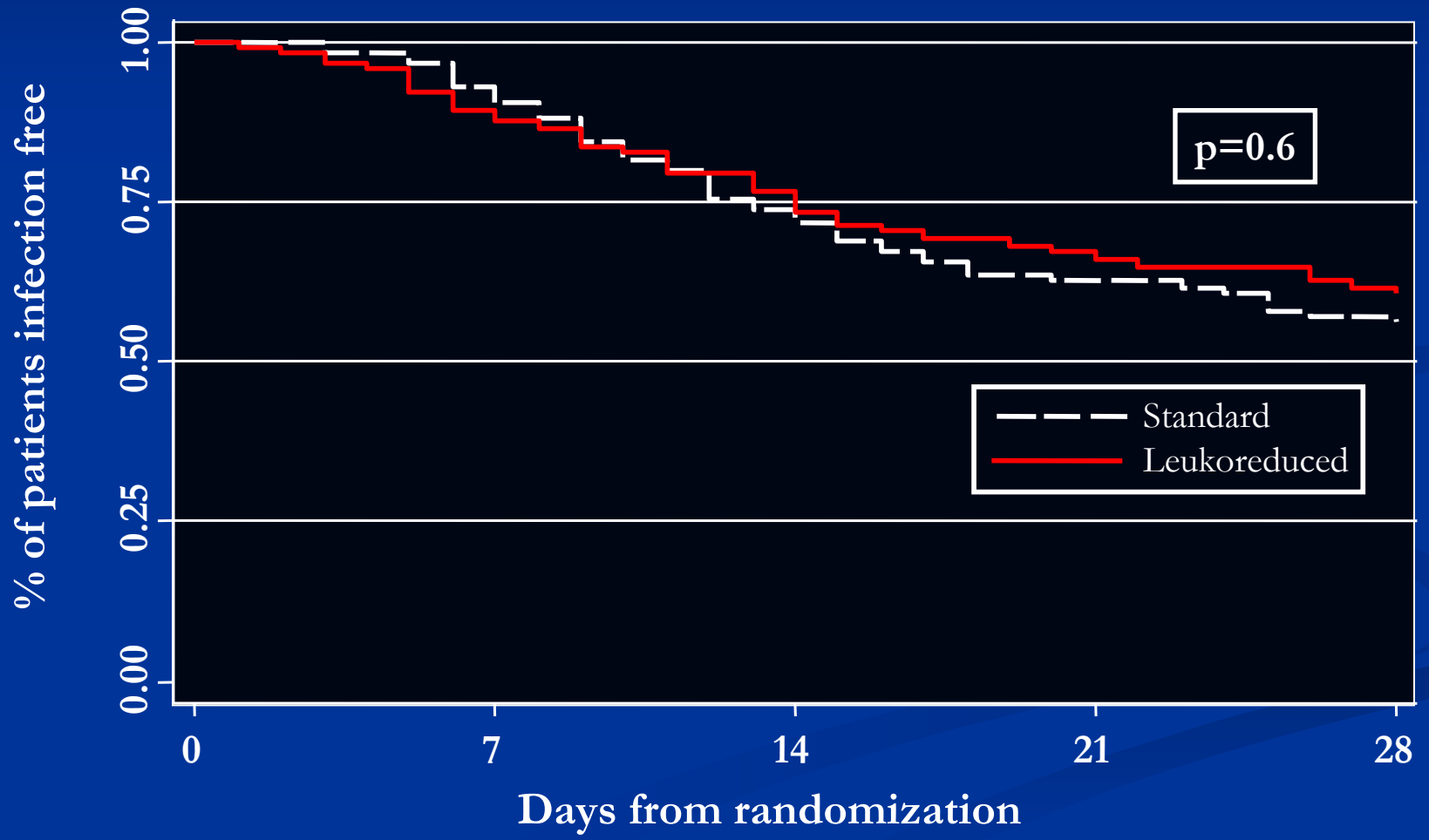
	RR of infection (95% CI)
Shock status	
No shock	1.04 (0.56-1.9)
Shock	0.74 (0.40-1.36)
Massive transfusion	
<6 units/48 hrs	0.91 (0.53-1.6)
≥6 units/48 hrs	0.84 (0.44-1.6)
ED lactate	
<2.5	0.92 (0.44-1.9)
≥2.5	0.79 (0.52-1.4)
Injury severity score	
<25	0.87 (0.45-1.7)
≥25	0.92 (0.54-1.6)

*Relative risk of infection in patients received leukoreduced transfusion compared to those received standard transfusion

Secondary endpoints

	Standard	**Leukoreduced**	**RR** (95% CI) or p-value
Mortality (ITT)			
Hospital	27 (16)	29 (19)	1.2 (0.72-1.9)
28-day	26 (15)	29 (19)	1.2 (0.74-1.9)
Median length of stay			
Hospital	13 (6-25)	12.5 (6-21)	0.49
ICU	3 (0.7-11)	4 (1-10)	0.59
Ventilator days	2.5 (1-10)	3 (1-8.5)	0.90
MOF Score	5.0 (3.6)	5.21 (3.3)	0.65

Time to event analysis



Summary

- No measurable clinical effect in this high risk population requiring transfusion
  - Infectious complications
  - Multiple organ failure
  - Resource utilization

Conclusions

- Differences across studies
  - Baseline risk of infection
  - Differences in patient population/immunoinflammatory state
  - Study design
  - Sample size
- Sample size required to detect RR of 0.8 with 80% power
  - 996 patients per group